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Channelopathic Pain: A Growing but Still Small List of Model Disorders

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In this issue of *Neuron*, Kremeyer et al. describe a gain-of-function mutation of TRPA1 that produces a painful disorder, familial episodic pain syndrome. This discovery enlarges the list of ion channels that, when mutated, produce pain. The growing universe of "channelopathic pain" presents some interesting overarching concepts and questions.

When C.S. Lewis described pain as "God's megaphone," he was referring to psychological pain. Physical pain, however, commands attention when it is present, and can be incapacitating. Pain occurs frequently and can be long-lasting and severe, for example, in association with diabetic neuropathy, postherpetic neuralgia, nerve injury, and traumatic limb amputation. Pain in these disorders is often unresponsive or only partially responsive to existing pharmacotherapies, so there is a pressing need for the development of more effective pain medications. In this issue of *Neuron*, Kremeyer et al. (2010) present a comprehensive analysis that links a gain-of-function mutation of TRPA1, a nonselective cation channel that functions as a sensor of environmental irritants, to a familial pain syndrome. This important study extends the universe of human "channelopathic" pain syndromes caused by ion channel mutations beyond the now well-established pain disorders associated with mutations of SCN9A, the gene that encodes voltage-gated sodium channel $Na_V1.7$.

As described by Kremeyer et al., a point mutation in the S4 transmembrane segment of TRPA1 produces a syndrome characterized by bouts of severe upper body pain, triggered by physical stress, cold, or fasting. These observations suggest that, for at least some painful disorders, TRPA1 antagonists may be useful as therapeutic agents, but they also raise interesting questions. The striking topographic pattern of pain affecting the arms and trunk is unusual and as enigmatic as the distal limb pain or lower body pain seen with $Na_V1.7$ channelopathies described below. We do not yet understand why, in these cases, a mutation of an ion channel that is expressed widely within primary sensory neurons should produce a spatially restricted pattern of pain. Possible explanations include regional expression of the mutated channel within sensory neurons innervating the affected part of the body, or a focal pattern of access to modulatory subunits or activating ligands. Alternatively, spatially differentiated patterns of expression of *other* channels in sensory neurons might modulate the response of these cells to the presence of the mutant channel. Different levels of expression of $Na_V1.8$ have been shown, for example, to exert a powerful cell background effect that strongly influences the impact of $Na_V1.7$ mutations on excitability in different types of neurons (Rush et al., 2006).

Discovery of this new syndrome enlarges the universe of ion channel mutations that can cause chronic somatic pain (Table 1). Since 2004, several dozen different mutations of sodium channel $Na_V1.7$ have been shown to cause three distinct clinical syndromes in humans (Dib-Hajj et al., 2010). Dominant gain-of-function missense mutations in $Na_V1.7$ cause inherited erythromelalgia (Yang et al., 2004), which is characterized by episodes of excruciating burning pain and redness in the distal extremities, triggered by mild warmth. In almost all cases, these mutations shift activation in a hyperpolarizing direction, slow deactivation, and increase the channel's response to slow subthreshold depolarizations (Cummins et al., 2004). A second syndrome, called paroxysmal extreme pain disorder (PEPD), is characterized by perirectal, periocular, and perimandibular pain, triggered by perineal stimulation, and is caused by another set of dominant gain-of-function mutations of $Na_V1.7$, which impair inactivation; as a result of the inactivation defect, these mutant channels produce an enhanced persistent current, which in many cases is reduced by the sodium channel blocker carbamazepine, a result that explains the favorable response of patients with PEPD to treatment with this medication. Complementing this duo of gain-of-function syndromes, a recessive loss-of-function syndrome, $Na_V1.7$-related congenital insensitivity to pain, has now also been identified (Cox et al., 2006). In this disorder, affected individuals lack functional $Na_V1.7$ channels and do not feel pain, thus accruing painless fractures, painless burns, etc.

Thus far, causative mutations of other members of the TRP and sodium channel families, including $Na_V1.8$ and $Na_V1.9$ (which, like $Na_V1.7$, acts as a threshold channel, amplifying small depolarizing inputs), and of other types of channels, have not been reported in patients with chronic somatic pain. $Na_V1.8$ and $Na_V1.9$ are preferentially expressed within dorsal root ganglion neurons, particularly nociceptors, and it might have been expected that mutations in these channels would alter pain perception or produce chronic pain. The absence of reports of mutations

Table 1. Channelopathic Pain Syndromes

Disorder	Inheritance	Channel	Mutation	Effects on Channel	Clinical Phenotype
Inherited erythromelalgia (IEM)	autosomal dominant	$Na_V1.7$	missense	lower threshold for activation; enhanced response to subthreshold stimuli	attacks of burning pain and redness in distal extremities; triggered by mild warmth and exercise
Paroxysmal extreme pain disorder (PEPD)	autosomal dominant	$Na_V1.7$	missense	impaired inactivation; enhanced persistent current	episodic lower body, ocular, and jaw pain accompanied by flushing and other autonomic abnormalities
Channelopathy associated insensitivity to pain (CIP)	autosomal recessive	$Na_V1.7$	nonsense	loss of function of $Na_V1.7$	inability to sense pain
Familial episodic pain syndrome (FEPS)	autosomal dominant	TRPA1	missense	enhanced inward current on activation	episodic upper body pain, triggered by fasting, cold, or stress

of $Na_V1.8$ and $Na_V1.9$ linked to pain syndromes could represent an ascertainment bias, since families with inherited pain syndromes are very rare; patients with the known $Na_V1.7$- and TRPA1-related pain syndromes describe the pain as excruciating, and pain of this severity might interfere with reproductive behavior. But it also might be speculated that mutations of $Na_V1.8$ and $Na_V1.9$ are less likely to produce pain. The voltage-dependence of $Na_V1.8$ is shifted 20–30 mV in a depolarizing direction relative to other sodium channels. Thus, $Na_V1.8$ requires more depolarization to activate but is relatively resistant to inactivation; once activated, it contributes the majority of the inward transmembrane current underlying the rising phase of the action potential and supports repetitive firing in response to sustained depolarization (Renganathan et al., 2001). The presence of wild-type $Na_V1.8$ can support firing at very high frequencies within permissive cell backgrounds (Waxman, 2006), and it is possible that gain-of-function mutations of $Na_V1.8$ do not enhance the activity of nociceptors because other sodium channels such as $Na_V1.7$ set threshold in these primary sensory neurons, with still other conductances (such as potassium channels) or cell-specific modulation setting upper limits on firing frequency. $Na_V1.9$ has been shown to regulate nociceptor excitability. However, this channel has a substantial effect on excitability even when present at 20%–40% of its normal levels, and this effect reaches an asymptote at levels well below those seen in primary sensory neurons (Herzog et al., 2001), so that gain-of-function mutations might not always result in a significant increase in nociceptor threshold or firing rate.

Whether mutations of other ion channels can produce chronic pain is not yet clear. Nociceptors express multiple ion channels, including some that are also present within CNS neurons. A mutation of sodium channel $Na_V1.3$ (Holland et al., 2008) that increases the persistent and ramp currents produced by this channel and induces hyperexcitability and spontaneous firing in hippocampal neurons (Estacion et al., 2010) has been shown to produce epilepsy. It is well-established that $Na_V1.3$ accumulates within neuromas, including painful human neuromas (Black et al., 2008). It would be interesting, in this regard, to know whether individuals housing this gain-of-function $Na_V1.3$ mutation have an increased propensity to develop neuropathic pain following nerve injury.

Finally, we are led to inquire as to whether sporadic cases of chronic pain, due to founder or de novo ion channel mutations, or pain syndromes associated with ion channel polymorphisms, are present within our population but have eluded detection. Several cases of sporadic erythromelalgia due to de novo mutations in SCN9A have been described (Dib-Hajj et al., 2010). Whether other mutations in $Na_V1.7$, in other sodium or TRP channels, or in other ion channels, would be identified via DNA profiling of larger numbers of patients with sporadic pain syndromes is not yet clear. A polymorphism of SCN9A, which produces the R1150W substitution in $Na_V1.7$, is present in more than 15% of control Caucasian chromosomes and has been shown to increase nociceptor excitability (Estacion et al., 2009). This polymorphism has now been linked in genome-wide association studies to enhanced pain sensitivity and an apparent increase in pain associated with disorders such as osteoarthritis, spinal root nerve injury, and phantom pain after limb amputation (Reimann et al., 2010). Other polymorphisms that alter pain perception, or the likelihood of developing chronic pain in various injury or disease states, are probably lurking within the human genome.

Neuroscientists have traditionally categorized pain as ''nociceptive'' (triggered by the presence of a noxious stimulus), ''neuropathic'' (due to dysfunction of the nervous system), or ''inflammatory'' (resulting from aberrant inflammatory activation of nociceptors). An increasing number of peripheral injuries have been shown to trigger changes in channel expression and excitability of neurons along the pain-signaling pathway, raising the question of whether most chronic pain has a neuropathic component. The discovery of a growing list of pain disorders, produced by mutations of ion channels, indicates that some pain disorders are driven by *intrinsic* gain-of-function changes in ion channels, and adds

primary (as opposed to secondary or acquired) channelopathies as causes of pain. Thus at least a few pain disorders can be considered to be "channelopathic." These disorders provide us with important model diseases in humans. The borders remain blurry, however, since ion channel genes may contain polymorphisms such as the R1140W $Na_V1.7$ substitution that are present in control populations but render pain-signaling neurons hyperexcitable, lowering pain threshold and possibly enhancing the effect of environmental or epigenetic changes.

Irrespective of these nosologic considerations, a growing list of channelopathies is helping us to make a translational leap in which we are beginning to unravel, molecule by molecule, the drivers of human pain. The list is still small, but each addition points toward a potential therapeutic target. Ultimately, this molecular dissection of human pain may enable us to mute "God's megaphone."

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Are Presynaptic Proteins Predisposed to Self-Assemble?

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Tight control of synapse formation ensures that neurons connect to appropriate targets. In this issue of *Neuron*, Klassen et al. identify ARL-8 GTPase as a regulator of presynaptic assembly. Without ARL-8, presynaptic material aggregates en route to its destination, suggesting that ARL-8 acts like a dispersant to prevent premature synaptic assembly in the axon.

Much attention has been paid to signals that initiate synaptogenesis. Contact between an axon and its proper target causes the postsynaptic membrane to accumulate receptors and scaffolding and causes the presynaptic varicosity to acquire an active zone and vesicle cluster (Jin and Garner, 2008; Owald and Sigrist, 2009). But focusing on signals for synapse building can overlook two equally important aspects of synaptogenesis: the infrastructure of the neuron that delivers the building materials to their site of assembly and the negative control mechanisms that prevent synapses from assembling where they should not. In this issue of *Neuron*, Klassen et al. (2010) describe a *C. elegans* mutant that highlights these aspects of synaptogenesis and points to a mechanism for restricting presynaptic specializations to their proper positions.

Presynaptic proteins are synthesized in the soma and transported along axons by specialized motors. The components travel in at least two classes of transport vesicle. One contains the components of synaptic vesicles and a second, often called a piccolo/bassoon transport vesicle, contains components of the active zone (Jin and Garner, 2008; Owald and Sigrist, 2009). These components are delivered principally by the kinesin-3 motors, which are distinct from those that support axon outgrowth and pathfinding (Pack-Chung et al., 2007). Disruption of this transport can prevent synapse